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Iron-Mediated [3 + 2] or [3 + 3] Annulation of 2-(2-(Ethynyl)phenoxy)-1-arylethanones: Selective Synthesis of Indeno[1,2-*c*]chromenes and 5*H*-Naphtho[1,2-*c*]chromenes

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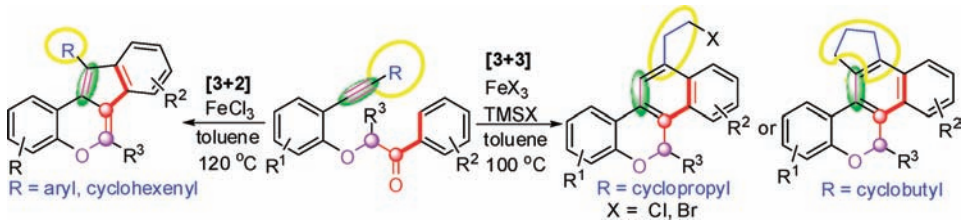
ABSTRACT



An iron-mediated tandem annulation strategy has been developed for the synthesis of numerous functional indeno[1,2-*c*]chromenes and 5*H*-naphtho[1,2-*c*]chromenes. This work is the first to disclose an iron-mediated method through sequential electrophilic addition of a ketone to an alkyne and annulation tandem reaction. Importantly, a halide is introduced into the products by a ring-opening process among the annulation of alkynylcyclopropanes, which makes the methodology more attractive for organic synthesis.

Transition metal-catalyzed annulation reactions provide attractive and efficient routes to the construction of the polycyclic carboaromatic and heteroaromatic skeletons.[1−4] However, regio- and chemoselectivity are unsatisfactory, and inaccessible substrates are necessary in many cases. For these reasons, versatile and efficient methodologies to synthesize these compounds with selective control of substitution patterns using readily accessible building blocks are still needed. Recently, transition metal-catalyzed [4 + 2] benzannulations of alkynes with carbonyl groups have been proven as a powerful tool to polycyclic aromatic compounds, and most were realized by the metal activation of the alkyne moiety under neutral conditions (Scheme 1).[3,4] We have also reported a novel protocol under basic conditions using $FeCl_3$ catalyst and 2-(2-ethynyl)phenoxy)-1-arylethanone substrates in MeCN that proceeds via a [4 + 2] cyclization/ring-opening process to afford naphthalen-1-ol derivatives in good yields.[5] In light of these results, we have decided to broaden this

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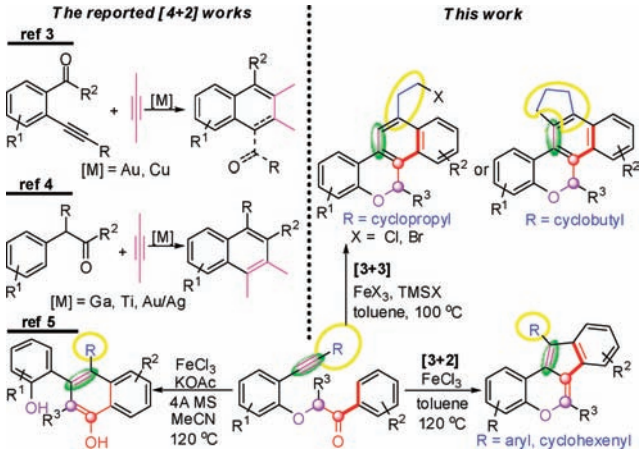
Scheme 1. Annulation of Alkynes with Carbonyl Groups



research under neutral conditions. Here, we report an unprecedented iron-mediated intramolecular annulation of 2-(2-(ethynyl)phenoxy)-1-arylethanones under neutral conditions through intramolecular [3 + 2] or [3 + 3] cyclization of an alkyne with a carbonyl group to produce polycyclic heteroarenes; indeno[1,2-c]chromenes and 5*H*-naphtho[1,2-*c*]chromenes can be selectively accessed by judicious choice of substituents at the terminal alkyne (Scheme 1).[6,7]

Under neutral conditions, no reaction was observed from 1-phenyl-2-(2-(phenylethynyl)phenoxy)ethanone (**1a**) with 20 mol % $FeCl_3$ in the reported effective MeCN solvent (entry 1, Table 1).[5,8] Interestingly, an expected [3 + 2] annnulation reaction took place in toluene although the yield of the

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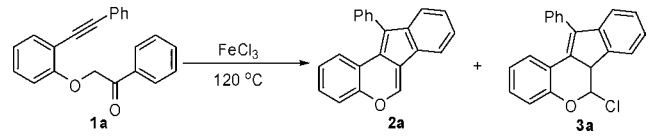
Table 1. $FeCl_3$-Mediated Synthesis of Indeno[1,2-c]chromenes[a]



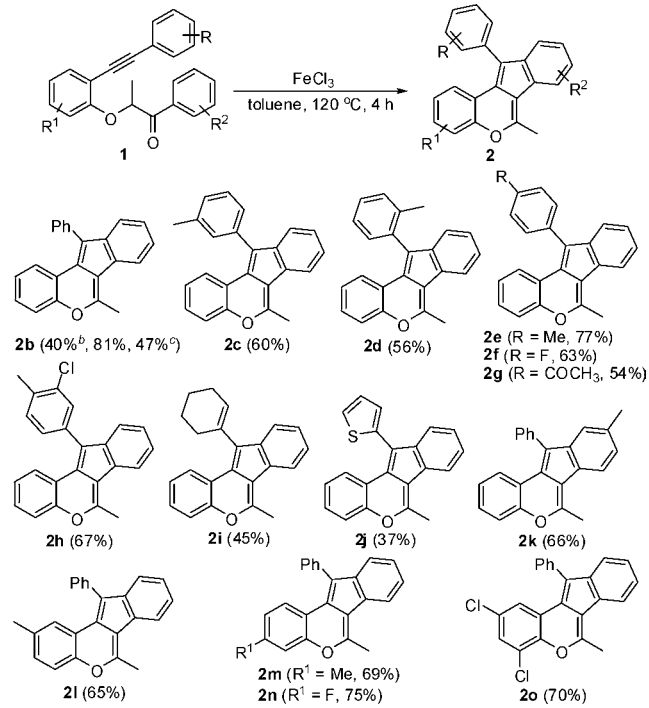
				isolated yield (%)	
entry	$FeCl_3$ (mol %)	solvent	*t* (h)	**2a**	**3a**
1	20	MeCN	48	trace	0
2	20	toluene	48	18	trace
3	40	toluene	4	48	25
4	60	toluene	4	45	20
5	100	toluene	4	42	26

[a] Reaction conditions: **1a** (0.3 mmol) and solvent (2 mL) at 120 °C.

desired product **2a** was low (entry 2). The $FeCl_3$ loading was subsequently examined (entries 3−5). We were pleased to find that at 40 mol % $FeCl_3$ the yield of **2a** was enhanced to 48% together with another chloro-addition annulation product **3a** in 25% yield (entry 3). However, identical results were obtained even using 60 or 100 mol % $FeCl_3$ (entries 4 and 5).

To shift the selectivity toward products **2**, methyl-substituted substrates were employed for the reaction (Scheme 2). As

Scheme 2. $FeCl_3$-Mediated [3 + 2] Annulation[a]



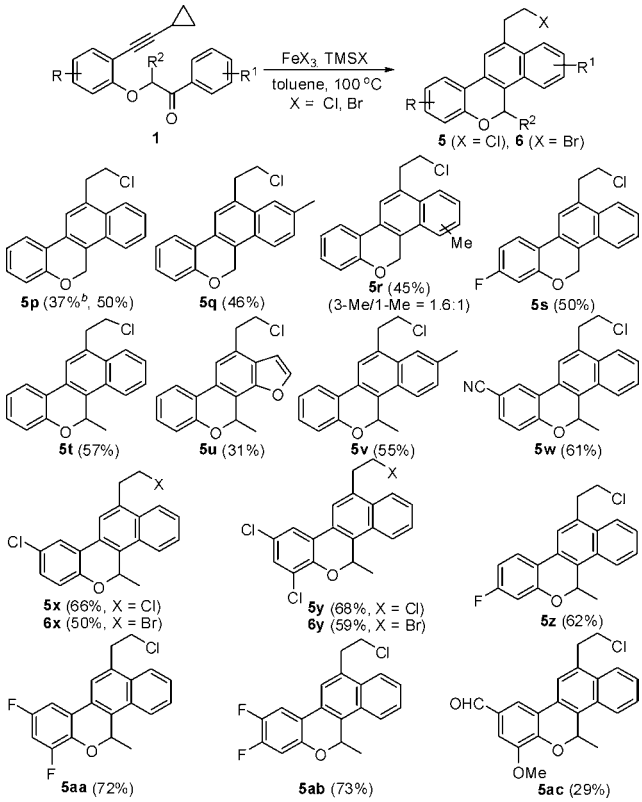
[a] Reaction conditions: **1** (0.3 mmol), $FeCl_3$ (100 mol %), and toluene (2 mL) at 120 °C for 4 h. [b] $FeCl_3$ (40 mol %). A cyclization/hydrolysis product **4b**, (2-methyl-3-phenyl-2*H*-chromen-4-yl)(phenyl)methanone, was isolated in 44% yield. [c] At 100 °C.

expected, product **2b** was obtained in 40% yield and no chloro-addition annulation product **3b** was observed using

40 mol % $FeCl_3$. However, the other cyclization/hydrolysis product **4b**, (2-methyl-3-phenyl-2*H*-chromen-4-yl)(phenyl)-methanone, was isolated in 44% yield. Gratifyingly, product **2b** was obtained alone in 81% yield when 100 mol % $FeCl_3$ was added. The reaction temperature has a fundamental influence on the reaction: the yield of **2b** was reduced to 47% at 100 °C. We were delighted to disclose that both electron-rich and electron-deficient arylalkynes were successfully annulated with 100 mol % $FeCl_3$ at 120 °C to afford indeno[1,2-*c*]chromenes **2c**−**2h** in moderate yields, although the steric hindrance and electron-deficient aryl groups lowered the substrate activity (**2d** and **2g**). Notably, the introduction of an olefin or a heterocycle into this system makes this methodology more useful for the preparation of pharmaceuticals and nature products (**2i**−**2j**). The same conditions were also consistent with substrate bearing a *p*-Me group on the aryl ring of the arylethanone moiety (**2k**). For substrates with a methyl, a fluoro or dichloro groups on the aromatic ring of the phenoxy moiety, the corresponding indeno[1,2-c]chromenes **2l**−**2o** were also obtained in good yields at 100 mol % $FeCl_3$.

For alkynylcycloalkanes,[9] to our surprise, the ring-opening and cyclization tandem reactions took place leading to 5*H*-naphtho[1,2-*c*]chromenes (Schemes 3 and 4). As summarized

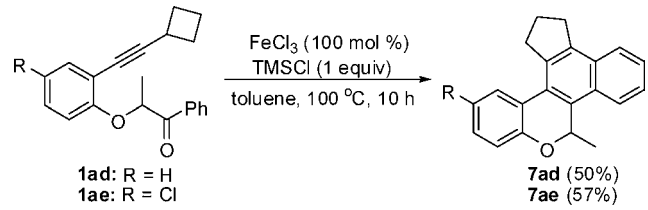
Scheme 3. FeX_3-Mediated [3 + 3] Annulation[a]



[a] Reaction conditions: **1** (0.3 mmol), $FeCl_3$ (100 mol %), TMSX (1 equiv) and toluene (2 mL) at 100 °C for 4 h. [b] Without TMSCl.

in Scheme 3,[8] treatment of 2-(2-(cyclopropylethynyl)phenoxy)-1-phenylethanone with 100 mol % $FeCl_3$ in toluene

Scheme 4. Sequential [3 + 3] Annulation and Friedel−Crafts Reaction



at 100 °C afforded the desired 12-(2-chloroethyl)-5*H*-naphtho[1,2-*c*]chromene (**5p**) in 37% yield. After a series of trials, we found that TMSCl could promote the reaction; the yield of **5p** was enhanced to 50% in the presence of 1 equiv of TMSCl. Subsequently, substituents on the aromatic ring of the arylethanone moiety were examined in the presence of $FeCl_3$ and TMSCl (**5q**, **5r** and **5v**). Substrates bearing a *p*- or *m*-methyl group afforded the corresponding products **5q**, **5r** and **5v** in moderate yields; two regioselective **5r** were isolated from *m*-methyl-substituted substrate with 1.6:1 ratio, and substrate with another methyl group at the α-position of ketone provided the best yield (**5v**). Therefore, a variety of α-methyl-substituted substrates were tested (**5t**−**5ac**, Scheme 3). Gratifyingly, the furan ring was suitable to construct an interesting benzofuro[7,6-c]chromene skeleton (**5u**). Substituents, such as cyano and halo groups, on the aromatic ring of the phenoxy moiety were uniformly well tolerated (**5w**−**5ab**, Scheme 3). Chloro-substituted substrate, for instance, successfully underwent the reaction with $FeCl_3$ and TMSCl in 66% yield (**5x**). Interestingly, this chloro-substituted substrate could react with $FeBr_3$ and TMSBr, producing the corresponding bromo-addition product **6x** in 50% yield. Another substrate with dichloro groups also reacted smoothly with either $FeCl_3$ or $FeBr_3$ in satisfactory yields (**5y** and **6y**). Notably, substrate having both a formyl and a methoxy groups was compatible (**5ac**).

Alkynylcyclobutanes are also viable substrates for the ring-opening and annulation reaction (Scheme 4). Surprisingly, the reaction of substrate **1ad** (0.3 mmol) with $FeCl_3$ (100 mol %) and TMSCl (1 equiv) provided a Friedel−Crafts alkylation product **7ad**, not the chloro-addition product.

(8) See the Supporting Information for details, including Tables S1−S2.

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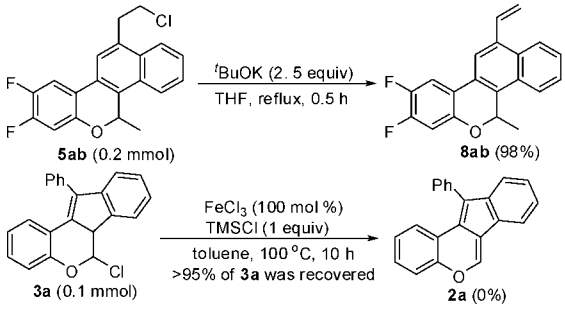
Moreover, product **7ae** was likewise obtained in 57% yield from another cyclobutane **1ae**.

The products **5** and **6** with a halo group provide an attractive and useful route to introduce new groups into these systems; dehydrohalogenation of product **5ab** by *t*-BuOK furnished alkene **8ab** in quantitative yield (eq 1).[10]

A controlled experiment showed that product **3a** could not be converted to product **2a** under the standard conditions (eq 2).



We envisioned a possible mechanism as outlined in Scheme 5 on the basis of the present results.[3,4,6−9] Initially, coordination of $FeCl_3$ to substrate **1** activates the alkyne moiety (intermediate **A**), followed by sequential electrophilic addition of a ketone and $FeCl_3$ to an alkyne affords intermediate **B**.[3] Electrophilic addition to an aromatic ring and ring-opening afford intermediate **C**.[4] Nucleophilic addition among intermediate **C** yields intermediate **D**. Dehydroxylation and rearrangement of intermediate **D** results in product **5**. Notablely, the Friedel−Crafts alkylation of products **5** and **6** can not take place because the construction of a highly strained four-membered ring is not favored in this system.

For aryl or vinyl alkynes (Scheme 2), the electrophilic addition among intermediate **B′** provides intermediate **C′**,[3] followed by dehydroxylation and rearrangement furnishes product **2**. Product **3a** is generated from dehydroxylation/chloro-addition of intermediates **C′**.

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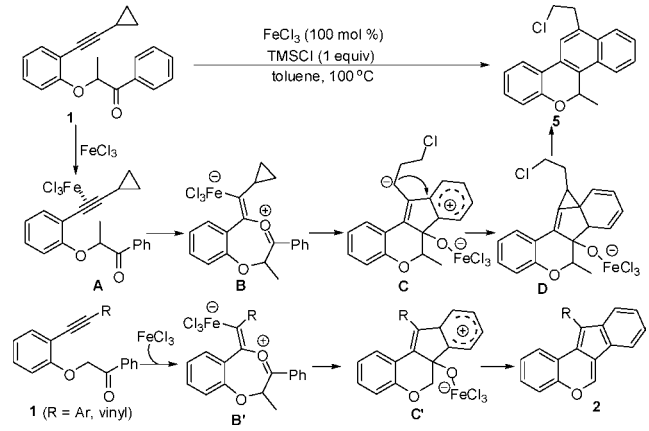
Scheme 5. Working Mechanisms



In summary, we have demonstrated that by application of an iron-mediated tandem annulation strategy numerous functional indeno[1,2-c]chromenes and 5*H*-naphtho[1,2-*c*]chromenes could be readily synthesized from 2-(2-(ethynyl)phenoxy)-1-arylethanones. This work is the first to disclose an iron-mediated method through sequential electrophilic addition of a ketone to an alkyne and annulation tandem reaction. Importantly, a halide is introduced into the products by a ring-opening process among the [3 + 3] annulation reactions of alkynylcyclopropanes, which makes the methodology more attractive for organic synthesis. Work to extend the reaction and study the detailed mechanism is currently underway.

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Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products; typical procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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